Epidemiologic risk factors for lung cancer in never smokers in australia and chin...

Environmental tobacco smoke

Ever since active tobacco smoking was well documented as the major and enormous cause of lung cancer, environmental tobacco smoke (ETS) has been one of the most widely studied risk factors for LCINS.(1) ETS is produced by quite a complicated mechanism. As the mainstream smoke is being inhaled by the active smoker, a stream of smoke is released into the air between the puffs known as the side-stream smoke, which is mixed with the exhaled mainstream smoke along with air. These by-products of active cigarette smoking are the constituents of ETS, which is also commonly known as second-hand smoke, and inhalation of ETS is called passive smoking or involuntary smoking.(2)

ETS, like tobacco smoke, is a complex mixture of numerous compounds with concentrations varying with time and environment. Both mainstream smoke and side-stream smoke contain a similar range of chemicals, but they differ in the relative proportions and amounts. Many of these chemicals belong to the classes known to be genotoxic and carcinogenic, including the International Agency for Research on Cancer (IARC) group 1, 2A and 2B carcinogens. Some harmful compounds in side-stream smoke are more than 10 times concentrated than that found in mainstream smoke. This is due to differences in the burning conditions for mainstream and side-stream smoke, leading to the incomplete combustion of the latter. As a result, a higher concentration of carcinogens is emitted in side-stream smoke than mainstream smoke.(2) Also, the side-stream smoke is 3-4 times more toxic than mainstream smoke,(3) and when side-stream smoke ages after it moves into the air, it becomes 2-4 times more toxic than fresh side-stream

smoke.(4) The toxicity of ETS also depends on a variety of factors including the type of tobacco and other compounds in the cigarette, the proportion of burned tobacco producing mainstream and side-stream smoke, the volume and components of the air with which it mixes.(5)

While the biological mechanisms of how ETS could lead to the development of lung cancer have been well documented, the epidemiological studies to establish ETS as risk factor for lung cancer have not been as straight forward as they should be. Despite the carcinogens are at high concentration in the emitted side-stream and mainstream smoke, they are still at much lower doses compared with the mainstream smoke inhaled by the active smoker. As a result, the overall risk of carcinogenic and toxic compounds from ETS exposure has been low accordingly and the increased risk of lung cancer in never smokers could not be readily detected.(6) This has been generally shown by the evidence of current literature.

In a meta-analysis by Ni et al.(7) which examined the association of ETS with lung cancer risk among non-smoking women in Asia, Europe and North America, 41 published studies from 1997 to 2017 were included and the pooled risks were calculated based on the type of study. It was found that the relative risk (RR) and 95% confidence interval (CI) of lung cancer in non-smoking women exposed to ETS was 1. 17 (0. 94–1. 44) for cohort studies, the odds ratio (OR) and 95% confidence interval (CI) was 1. 35 (1. 17–1. 56) for case-control studies, and the pooled risk (95% CI) was 1. 33 (1. 17–1. 51) for both types of studies. This meta-analysis concluded that the summary RR estimate of the cohort studies was not statistically significant, and though the case-control studies provided a significant risk, the evidence based on

those studies was relatively weak due to recall bias and small sample sizes. Another recent meta-analysis by Sheng et al.,(8) which included 20 case-control studies to investigate the association of ETS with lung cancer among non-smoking adults in China, has shown that the risk of lung cancer being significantly higher for those exposed to ETS in general (OR: 1. 64, 95% CI: 1. 34–2. 01), and also significantly higher for women exposed to ETS at home. There was, however, no evidence of significant risk of lung cancer for men exposed to ETS at workplace, women exposed at workplace, or men exposed at home. Li et al. also assessed the association between long-term exposures to ETS and lung cancer incidence in China with meta-analysis (9) and reported that the pooled OR (95% CI) for ETS exposure from spouse, parents and work was 1. 153 (1. 000–1. 329), 2. 117 (1. 626–2. 755), and 1. 454 (1. 307–1. 618) respectively. As ETS exposure from parents resulted in the highest odds ratio, it raised the concerns of higher risk of childhood exposure than adulthood exposure. However, Fu et al.’s meta-analysis found that both childhood exposure and adulthood exposure were not statistically significant, with combined OR (95% CI) as 1. 37 (0. 98-1. 91) and 1. 34 (0. 97-1. 85) respectively.(10) Boffetta et al.’s meta-analysis also did not provide evidence of an increased lung cancer risk for ETS exposure (summary RR: 0. 91, 95% CI: 0. 80-1. 05) in adulthood and childhood.(11)

Nevertheless, some studies were able to provide clearer evidence to support the association between ETS and lung cancer. Taylor et al.’s meta-analysis evaluated 55 studies (7 cohort and 48 case-control) to calculate the pooled estimate of relative risk (RR) of lung cancer associated with ETS in never smoking women exposed to smoking spouses in North America, Asia and

Europe.(12) It was found that the overall pooled RR (95% CI) for never-smoking women exposed to ETS from spouses in the 3 regions was 1. 27 (1. 17–1. 37). The RR (95% CI) for North America was 1. 15 (1. 03–1. 28), Asia, 1. 31 (1. 16–1. 48) and Europe, 1. 31 (1. 24–1. 52).

As LCINS has been more common in women of East Asian ethnicity and recognised as a distinct disease entity,(13-16) it is proposed that different carcinogenic mechanisms work across various demographically distinct populations of never-smokers, involving an interaction between certain environmental/lifestyle risk factors and genetic susceptibility.(17) Several studies have been conducted to investigate the relationship between ETS exposure and gene mutation profiles in never-smokers. Ren et al.'s meta-analysis of 26 case-control studies demonstrated that the OR (95% CI) for the EGFR mutation in non-smokers relative to smokers was 4. 829 (3. 598–6. 482) with $P < 0.001$.(18) Soo et al. also examined the potential contribution of ETS to driver mutations and it was found that an increased ETS exposure was significantly associated with EGFR mutations in female never-smokers in an expanded cohort study involving participants in Japan, Korea, Singapore and United States.(19) Another study by Liang et al. found a positive correlation between ETS exposure duration and rate of EGFR mutation and concluded that ETS exposure might also be an inducing factor for EGFR mutations.(20) However, based on a multicentre case-control study, there was a negative association (though statistically insignificant) between childhood ETS exposure and the likelihood of EGRF mutation, and no association between adulthood exposure (at home or workplace) and EGFR mutation.(21)

In summary, when assessing the association between ETS and lung cancer in never-smokers, the relative risks derived from current studies are weak, and the results need to be interpreted with caution as there are many sources of bias and confounding factors which may lead to either underestimation or overestimation of the true relationship.

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